shown by Arg-Gln-Lys-Leu-Glu-Asp-Ser-Tyr-Arg-Phe-Gln-Phe-Phe-Gln-Arg-Asp-Ala-Glu-Glu-Leu (SEQ ID NO:1) and the molecular weight of which is from about 2K to about 240K, or a salt thereof with a pharmaceutically acceptable carrier.

Claims 16-19 have been canceled, without prejudice.

25. (amended) The method of claim 14, wherein inflammation of lacrimal or salivary glands is a symptom of Sjögren's syndrome.

REMARKS

In the Office Action dated October 19, 2002, claims 14, 16-19 and 25 are pending and stand rejected. In the above amendment, claim 14 has been amended to recite a method for preventing or treating Sjögren's syndrome which comprises administering to a patient a therapeutically effective amount of α-fodrin, a mutein thereof, an antigenic fragment available upon proteolysis of α-fodrin with a protease, which contains or comprises an amino acid sequence substantially shown by Arg-Gln-Lys-Leu-Glu-Asp-Ser-Tyr-Arg-Phe-Gln-Phe-Phe-Gln-Arg-Asp-Ala-Glu-Glu-Leu (SEQ ID NO:1) and the molecular weight of which is from about 2K to about 240K, or a salt thereof with a pharmaceutically acceptable carrier. Claims 16-19 have been cancelled without prejudice and incorporated into claim 14. Claim 25 has been amended to recite that inflammation of lacrimal or salivary glands is a symptom of Sjögren's syndrome. No new matter has been added. The above amendments have been made to expedite examination of this application.

In light of the above amendments and following discussions, applicants respectfully request that the outstanding rejections be withdrawn and the claims be allowed.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Claims 14, 16-19 and 25 are pending and stand rejected under 35 USC 112, first paragraph. It is the Examiner's position that the specification does not contain a written description that enables one of ordinary skill in the art to practice the invention. Applicants respectfully traverse this rejection.

It is the Examiner's position that it is not possible to treat an ongoing immune disease by providing the animal with a tolerance to one antigen because the autoimmune disease is usually caused by multiple antigens. The Examiner cites Wraith et al., (Cell 59: 247-255, 1989) at page 253, col. 1, as teaching that "Inhibition of the response restricted by one class II molecule may lead only to the escape to an autoimmune response to a separate epitope restricted by a different class II molecule." Applicants respectfully submit that Wraith is referring to one of the potential difficulties in using MHC "blocking" peptides to treat autoimmune diseases. Wraith teaches that this particular difficulty arises when the autoantigen has multiple distinct epitopes that are presented by different class II molecules of the MHC. Wraith uses experimental autoimmune encephalomyelitis (EAE) as a prototypical model for multiple sclerosis, an autoimmune disease. Thus, it appears that the problems associated with the system in Wraith may not be relevant to the present invention.

In contrast, the method of the present invention for preventing or treating Sjögren's syndrome was demonstrated using a different model, (Athymic NFS/sld mouse) which is specific for Sjögren's syndrome. This difference is readily recognizable to one of ordinary skill in the art. Thus, the teachings in Wraith do not support the Examiner's position that the specification does not contain a written description that enables one of ordinary skill in the art to practice the invention.

In addition, Wraith, et al. were able to find and describe two approaches for immunomodulation that may be useful for the design of therapeutic strategies for treating autoimmune diseases. In fact, the paper describes how peptide analogs can be designed that have normal or increased MHC binding properties and that fail to activate disease-inducing T cells. The paper also describes a peptide that is highly antigenic in vitro, but nonimmunogenic in vivo. They teach that it is feasible to use a synthetic peptide for immune intervention in an autoimmune disease. (See page 253, right column). Thus, Wraith supports applicants' position that one of ordinary skill in the art would recognize that the method of the present invention, i.e., for preventing or treating Sjögren's syndrome which comprises administering to a patient a therapeutically effective amount of α-fodrin, a mutein thereof, or an antigenic fragment α-fodrin fragment can be used to treat the Syndrome.

Applicants respectfully disagree with the Examiner's statement that applicants "misrepresented" the teachings of the Immunology text. Applicants respectfully submit that the Examiner has taken this sentence out of the context of the entire paragraph. The remainder of the paragraph states that recent studies have shown that neonatal mice can develop efficient immune responses. The text goes on the state that the tolerance to antigen may in fact be due to a protective Type-I response. Applicants respectfully refer the Examiner to the last 2 sentences of the last paragraph on page 171 of the text, and that continues to the following page.

The Examiner takes the position that Applicants failed to support the assertion that one of ordinary skill in the art can obtain immunochemically equivalent fragments by following the teachings of the specification. The Examiner cites Karin et al. as demonstrating that "substitution of a phenylalanine with alanine at position 89 resulted in an increase in T cell proliferation, binding affinity of the peptide and induction of experimental allergic encephalomyelitis (EAE) in rats, while the same amino acid substitution, a phenylalanine for an alanine, at position 90, resulted in the exact opposite results, decreased binding, T cell proliferation and no induction of EAE (see Table 1, in particular)." The Examiner cites this article as

teaching that the effects of amino acid changes on peptide-MHC binding, T cell proliferation and in vivo effects of said peptides is unpredictable.

Applicants respectfully disagree with the Examiner's interpretation of Karin. Karin describes a study of interactions between myelin basic protein (MBP) p87-99, class II MHC and T cell receptor (TCR), which is then used to design soluble inhibitors for therapy. Thus, Karin et al. were able to design a peptide inhibitor that antagonizes pathogenic T cells. This peptide was shown to reverse ongoing EAE with clinical paralysis. They also teach the use of TCR antagonists to prevent EAE. Specifically Karin found that three analogues could be used as therapeutic TCR antagonists capable of blocking EAE. (See p. 2229, col. 2.) Karin et al, further found that one of the antagonists did, in fact, prevent and reverse EAE. (See p. 2234, Col. 2, and page 2235, Col. 2). Furthermore, Karin specifically states, "We propose here that parenteral administration of modified native proteins devoid of encephalitogenic potential that antagonize TCR involved in the disease will be an advantageous strategy for the therapy of MS." (Page 2235, Col. 2, last line.)

Thus, although Karin uses a different system, i.e., an EAE model to study MS, this reference actually supports Applicants' position that one of ordinary skill in the art would readily be able to practice the methods of the present invention based on the teachings contained in the specification.

Finally, the Examiner discounts the experimental data provided in the last response because the information was not supplied in the form of a declaration. The Examiner further objected to the experiments because he states that it is not clear that the experiments performed where done in accordance to the teachings of the specification. The Examiner also objected that it was not clear that the fragment used in the experiments was the same as disclosed in the specification. Applicants respectfully disagree with the Examiner's position. The data specifically states that the α-fodrin fragment protein obtained in Example 2 was investigated in accordance with Example 4, with changes in administration times.

However, in order to expedite examination and allowance of this application, Applicants provide herewith a Declaration of Dr. Yoshio Hayashi, one of the inventors. The test set forth in the Declaration was prepared and performed in accordance with the teachings in the specification. The experimental conditions are described in paragraphs 3 (1) and (2) of the Declaration. The results of the experiment are set forth in paragraph 3(3) and demonstrate the inhibitory effect of human α-fodrin fragment protein on on-going Sjögren Syndrome.

The NFS/sld mouse used in the experiment (and in the application) provides a known model of Sjögren Syndrome. As described in the Declaration, growth of lesions in the submandibular, parotid and lacrimal glands in these mice is indicative of Sjögren Syndrome. These symptoms are evident after 4 weeks in such a model. Thus, a decrease in these lesions from a treatment after 5, 6 and 7 weeks in these mice is indicative of an effective treatment.

As stated in the Declaration, the results of this experiment show that administration of the human α-fodrin fragment protein inhibited the growth of lesions in the submandibular, parotid and lacrimal glands. Thus, treatment with human α-fodrin fragment protein inhibited the symptoms of Sjogren Syndrome. In contrast, the control mice that received only glutathione S-transferase, showed lesion growth.

The results set forth in the Declaration, and in Example 4 of the patent application, confirm that treatment with the human α-fodrin fragment protein (obtained in accordance with Example 2) has a suppressive effect on ongoing Sjögren Syndrome and the onset of Sjögren Syndrome.

The Declaration shows that the human α-fodrin fragment protein described in the present application and obtained through the methods described in Example 2 therein is a useful prophylactic and therapeutic agent for autoimmune disease, particularly Sjogren Syndrome.

In view of the above discussion and amendment, it is respectfully submitted that the present application is in condition for allowance. Therefore, an early reconsideration and allowance are respectfully requested.

Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

Respectfully submitted,

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"VERSION WITH MARKINGS TO SHOW CHANGES MADE."

IN THE CLAIMS

Please amend the claims as follows:

14. (amended) A method for preventing or treating Sjögren's syndrome which comprises administering to a patient a therapeutically effective amount of α-fodrin, a mutein thereof, an antigenic fragment ~~thereof~~ available upon protcolysis of α-fodrin with a protease, which contains or comprises an amino acid sequence substantially shown by Arg-Gln-Lys-Leu-Glu-Asp-Ser-Tyr-Arg-Phe-Gln-Phe-Phe-Gln-Arg-Asp-Ala-Glu-Glu-Leu (SEQ ID NO:1) and the molecular weight of which is from about 2K to about 240K, or a salt thereof with a pharmaceutically acceptable carrier.

Please cancel claims 16-19, without prejudice.

25. (amended) The method of claim 14, wherein ~~Sjögren's syndrome is a symptom of~~ inflammations of lacrimal or salivary glands is a symptom of Sjögren's syndrome.